How slow, deep breaths induce tranquility

By Bruce Goldman

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It’s a question that has never been answered by science, until now.

In a new study, researchers at the School of Medicine and their colleagues have identified a handful of nerve cells in the brainstem that connect breathing to states of mind.

A paper describing the findings was published March 31 in Science. Mark Krasnow, MD, PhD, professor of biochemistry, is the senior author. The lead author is former Stanford graduate student Kevin Yackle, MD, PhD, now a faculty fellow at UC-San Francisco.

Medical practitioners sometimes prescribe breathing-control exercises for people with stress disorders. Similarly, the practice of pranayama — controlling breath in order to shift one’s consciousness from an aroused or even frantic state to a more meditative one — is a core component of virtually all varieties of yoga.

“This study is intriguing because it provides a cellular and molecular understanding of how that might work,” Krasnow said.

Tiny cluster of neurons

The tiny cluster of neurons linking respiration to relaxation, attention, excitement and anxiety is located deep in the brainstem. This cluster, located in an area Krasnow calls the pacemaker for breathing, was discovered in mice by study co-author Jack Feldman, PhD, a professor of neurobiology at UCLA, who published his findings in 1991. An equivalent structure has since been identified in humans.

“The respiratory pacemaker has, in some respects, a rougher job than its counterpart in the heart,” said Krasnow, who is also a Howard Hughes Medical Institute investigator. “Unlike the heart’s one-dimensional, slow-to-fast continuum, there are many distinct types of breaths: regular, excited, sighing, yawning, gasping, sleeping, laughing, sobbing. We wondered if different subtypes of neurons within the respiratory control center might be in charge of generating these different types of breath.”

On that hunch, Yackle searched through public databases to assemble a list of genes that are preferentially activated in the part of the mouse brainstem where the breathing-control center resides. This center’s technical term is the pre-Bötzinger complex, or preBötC.

He pinpointed a number of such genes, allowing the investigators to identify more than 60 separate neuronal subtypes, physically differentiated by their gene-activation signatures but coexisting in the preBötC-like well-stirred spaghetti strands. The scientists were able to use these genes, and the protein products for which they are recipes, as markers allowing them to zero in on the different neuronal subtypes.

Knocking out neurons

Now the scientists could systematically assess the role of each neuronal subtype in laboratory mice.

With advanced technologies, they could selectively destroy any one of these neuronal subtypes — and only that subtype — based on its unique signature of active genes. Then they could observe how this particular subtype’s loss affected the animals’ breathing.

In 2016, in collaboration with Feldman, they succeeded in isolating a subpopulation of neurons in the preBötC that explicitly controls inspiration and expiration.

Stores of monounsaturated fat help pudgy worms outlive skinny worms

By Krista Conger

Pudgy roundworms storing a particular type of fat live longer than their more svelte counterparts, according to a study by researchers at the School of Medicine.

This fatty buildup, and the subsequent increase in the worms’ life span, can be simulated simply by feeding the animals monounsaturated fatty acids like those found in olive oil. Because many species share similar patterns of fat metabolism, it’s possible that the findings could extend to other animals, including humans, the researchers believe.

The finding suggests that accumulating a specific type of fat can actually be beneficial. It came as a surprise to the researchers because severe caloric restriction has also been shown to extend the life span of many animals.

“We have known for some time that metabolic changes can affect life span, but we expected the long-lived animals in our study would be thinner,” said Anne Brunet, PhD, professor of genetics. “Instead, they turned out to be fatter. This was quite a surprise.”

Anne Brunet and her team were surprised to find that pudgy roundworms with stores of monounsaturated fat outlived thinner worms.

By Jennifer Yuan

Lucile Packard Children’s Hospital Stanford has received a gift of $50 million from Gordon and Betty Moore to deliver exceptional patient care and advance research that improves the health of children with heart disease.

The Moores’ donation is the largest private gift to Lucile Packard Children’s Hospital Stanford since the hospital’s founding donation from David and Lucile Packard.

In honor of the new gift, Packard Children’s internationally renowned Children’s Heart Center will be named the Betty Irene Moore Children’s Heart Center. The gift provides funding for clinical and research facilities, an endowment for the center’s highest strategic priorities and endowed positions for the faculty to lead specialized care and research.

Gordon Moore is co-founder of Intel Corp. He and his wife, Betty, are also founders of the Gordon and Betty Moore Foundation, which works to create positive outcomes for future generations. They are longtime supporters of Packard Children’s and previously made gifts to enable the hospital’s $21,000-square-foot expansion, which is now nearing completion.

The Moores were motivated to make their latest gift
Ultrasound and microbubbles flag malignant cancer in humans

By Jennie Dusheck

A team led by researchers from the School of Medicine has demonstrated a way to diagnose cancer without resorting to surgery, raising the possibility of far fewer biopsies.

For the study — a first-in-humans clinical trial — which was published online March 14 in the Journal of Clinical Oncology, women with either breast or ovarian tumors were injected intravenously with microbubbles capable of binding to and identifying cancer.

Jürgen Willmann, MD, a professor of radiology at Stanford, is lead author, and Sanjiv “Sam” Gambhir, MD, PhD, professor and chair of radiology, is the senior author.

For the study, 24 women with ovarian tumors and 21 women with breast tumors were intravenously injected with the microbubbles. Ultrasound imaging was performed to obtain an ordinary ultrasound to image the tumors for about a half-hour after injection. The high-tech bubbles clustered in the blood vessels of tumors that were malignant, but not in those that were benign.

The ultrasound imaging of patients’ bubble-labeled tumors allowed Dupuy to biopsy and pathology studies that confirmed the accuracy of the diagnostic microbubbles.

What are microbubbles?

Medical microbubbles are spheres of phospholipids, the same material that makes up the membranes of living cells. The bubbles are 3 to 4 microns in diameter, a little smaller than a red blood cell, and filled with a harmless mixture of perfluorobutane and nitrogen gas.

Ordinary microbubbles have been approved by the Food and Drug Administration and in clinical use for several years now. But such microbubbles, a kind of ultrasound “contrast agent,” have only been used to image organs like the liver by displaying the bubbles as they pass through blood vessels. Up to now, the bubbles couldn’t latch onto blood vessels of cancer in patients.

Safe but better microbubbles

The microbubbles used in this study were designed to bind to a receptor called KDR found on the tumor blood vessels of cancer but not in healthy tissue. Noncancerous cells don’t have such a receptor. Under ultrasound imaging, the labeled microbubbles, MBKDR, show up clearly when they cluster in a tumor. And since benign breast and ovarian tumors usually lack KDR, the labeled microbubbles mostly passed them by.

In this small, preliminary safety trial, the technique appeared to be both safe and very sensitive, said Willmann, who is chief of the Division of Body Imaging at Stanford. And it also works with ordinary ultrasound equipment. “So, there’s no new ultrasound equipment that needs to be built for this,” he said. “You can just use your regular ultrasound and turn on the contrast mode — which all modern ultrasound equipment has.”

Willmann said now that the phase-1 trial has shown that MBKDR contrast agent is safe for patients, his team is moving forward in a larger phase-2 trial. In that trial, the team will measure how well the combination of MBKDR and ultrasound differentiate cancer from noncancer in breast and in ovarian tumors. The team will also try to find out how small a tumor can be imaged using KDR microbubbles. Because the diagnostic approach can, in principle, be used with any kind of cancer that expresses KDR, they plan to image pancreatic cancer tumors as well.

One of the advantages of MBKDR, Willmann said, is that the bubbles remain attached to the tumors for several minutes and as long as half an hour — the longest time tested in the trial. That should give clinicians time to image both breasts or both ovaries without having to start over with a new injection of contrast agent.

If all goes as hoped, the KDR microbubbles could improve diagnoses and reduce unnecessary surgeries in women suspected of having breast or ovarian cancer.

“The difficulty with ultrasound right now,” Willmann said, “is that it detects a lot of lesions in the body that are benign. And that leads to many unnecessary biopsies and surgeries.”

Distinguishing benign and malignant tumors with harmless ultrasound imaging could save millions of patients from biopsies they don’t need, Willmann said.

“To decrease those unnecessary biopsies and surgeries would be a huge leap forward,” he said. “We could make ultrasound a highly accurate screening technology that is relatively low cost, highly available and with no radiation.”

And since ultrasound technology is accessible almost everywhere, he said, the technology could potentially help patients all over the world.

The work is an example of Stanford Medicine’s focus on precision health, the goal of which is to anticipate and prevent disease in the healthiest and precisely diagnose and treat disease in the ill.

Other Stanford-affiliated co-authors of the study are assistant professors of radiology, Amelia Lutz, MD, and research assistant Keerthi Valluru.

Gambhir is also director of the Canary Center for Cancer Early Detection at Stanford, director of the Molecular Imaging Program at Stanford and a member of Stanford Bio-X. Willmann is a member of Stanford Bio-X, the Molecular Imaging Program and the Canary Center. Lutz is a member of Stanford Bio-X.

Researchers from the Gemelli University Hospital in Rome are also co-authors of the study.

The research was supported by the National Institutes of Health, the Bracco Group and the Canary Foundation.

Stanford’s Department of Radiology also supported the work.

Stanford researchers seeking teens, young adults with autism for clinical trial of drug that may reduce aggressive behaviors

By Erin Digitalle

Researchers at the School of Medicine are seeking teenagers and young adults ages 14 to 21 to participate in a clinical trial of a compound, pregnenolone, that may reduce aggressive behaviors in autism spectrum disorder.

Irritability and aggressive behavior are the most common forms of autism and are also co-occurring problems. Some are the tumor blood vessels of cancer but not in healthy tissue. Noncancerous cells don’t have such a receptor. Under ultrasound imaging, the labeled microbubbles, MBKDR, show up clearly when they cluster in a tumor. And since benign breast and ovarian tumors usually lack KDR, the labeled microbubbles mostly passed them by.

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Without effective treatment, these behaviors can cause significant problems in daily life for people with autism and their families. But available treatments have drawbacks.

“The atypical antipsychotic medications we use to treat mood dysregulation in autism have a lot of side effects,” said lead investigator Antonio Hardan, MD, professor of psychiatry and behavioral sciences. “The long-term side effects can include diabetes and involuntary motor movements.

Pregnenolone is a neurosteroid that has previously been shown to alleviate symptoms of other psychiatric conditions such as schizophrenia. Neurosteroids are naturally occurring steroid hormones synthesized in the brain and other organs. Recently, researchers have begun to understand their roles in sending signals to nerves in the brain.

“The biology of neurosteroids in other psychiatric disorders has been studied for about 20 years, but in autism not much is known,” said study investigator Lawrence Fung, MD, PhD, an instructor in psychiatry and behavioral sciences. “This study will give us a chance to understand their role in the pathophysiology of autism. The trial may also enable the future development of biomarkers for autism, he said.

Some scientists hypothesize that individuals with autism have too much excitatory signaling or too little inhibitory signaling, or both, in their brain circuits. Metabolites of pregnenolone have been shown to increase inhibitory signaling. Thus, pregnenolone may benefit people with autism by “normalizing” the imbalance in excitatory versus inhibitory signaling; it could possibly help treat mood dysregulation, sensory abnormalities and social deficit.

“Pregnenolone is very benign and usually very well tolerated by large groups of people,” he said. “Pa- tients should know that the potential for benefit is modest, but we think it is still worth exploring its value in treating individuals with autism.”

Teens and young adults aged 14 to 21 with autism are eligible to enroll in the trial. Study participants will visit Stanford once every two weeks for the 14-week trial, but most of them will be randomized to receive either pregnenolone or placebo and will not know which compound they are taking until the 14-week period is over. After that, the subjects who receive placebo in the random- ized phase will have the option to start taking pregnenolone.

More information about the trial is available at http://med.stanford.edu/autism or by calling (650) 736-1235.
Nerve cells actively repress alternative cell fates, study shows

By Krista Conger

A neural cell maintains its identity by actively suppressing the expression of genes associated with non-neuronal cell types, including skin, heart, lung, cartilage and liver, according to a study by researchers at the School of Medicine.

It does so with a powerful repressor protein. “When this protein is missing, neural cells get a little confused,” said Marius Wernig, MD, associate professor of medicine and of pediatrics. “They become less efficient at transmitting nerve signals and begin to express proteins associated with other cell fates.”

The study marks the first identification of a near-global repressor that works to block many cell fates but one. It also suggests the possibility of a network of as-yet-untapped master regulators specific to each cell type in the body.

“The concept of an inverse master regulator, one that represses many different developmental programs rather than activating a single program, is a unique way to control cell and tissue identity, and a completely new paradigm as to how cells maintain their cell fate throughout an organism’s lifetime,” Wernig said.

Repressors

Myt1l is not the only protein known to repress certain cell fates. But most other known repressors specifically block only one type of developmental program, rather than many. For example, a well-known repressor called REST is known to block the neuronal pathway, but no others.

“Until now, researchers have focused only on identifying these types of single-lineage repressors,” said Wernig. “The concept of an ‘everything but’ repressor is entirely new.”

Wernig showed that it is possible to convert skin cells into functional neurons over the course of three weeks by exposing them to a combination of just three proteins that are typically expressed in neurons. This “direct reprogramming” bypassed a step called induced pluripotency that many scientists had thought was necessary to transform one cell type into another.

One of the proteins necessary to accomplish the transformation of skin to neurons was Myt1l. But until this study the researchers were unaware precisely how it functioned.

“We usually think in terms about what regulatory programs need to be activated to direct a cell to a specific developmental program, said Wernig. “So we were surprised when we took a closer look and saw that Myt1l was actually suppressing the expression of many genes.”

These genes, the researchers found, encode proteins important for the development of lung, heart, liver, cartilage and other types of non-neuronal tissue. Furthermore, two of the proteins, Notch and Wnt, are known to actively block neurogenesis in the developing brain.

Blocking Myt1l expression in the brains of embryonic mice reduced the number of mature neurons that developed in the animals. Furthermore, knocking down Myt1l expression in mature neurons caused them to express lower-than-normal levels of neural-specific genes and to fire less readily in response to an electrical pulse.

“A perfect team”

Wernig and his colleagues contrasted the effect of Myt1l with that of another protein called Ascl1, which is required to directly reprogram skin fibroblasts into neurons. Ascl1 is known to specifically induce the expression of neuronal genes in the fibroblasts.

“Together, these proteins work as a perfect team to funnel a developing cell, or a cell that is being reprogrammed, into the desired cell fate,” said Wernig. “It’s a beautiful scenario that both blocks the fibroblast program and promotes the neuronal program. My gut feeling would be that there are many more master repressors like Myt1l to be found for specific cell types, each of which would block all but one cell fate.”

Wernig is a member of Stanford’s Institute for Stem Cell Biology and Regenerative Medicine, Cardiovascular Institute, Child Health Research Institute, Cancer Institute, Neurosciences Institute and Bio-X.

Other Stanford co-authors of the paper are postdoctoral scholars Soham Chanda, PhD, Bo Zhou, PhD, Xuecai Ge, PhD, and Philip Brencecke, PhD; graduate students Cheen Ang, Thomas Vierbuchen and Daniel Fuentes; research assistant Sarah Grieder; undergraduate student Brandon Walker; professor of genetics Lars Steinmetz, PhD; and professor of molecular and cellular biology Thomas Sudhof, MD.

The research was supported by the German Research Foundation, the National Institutes of Health, the California Institute for Regenerative Medicine, the New York Stem Cell Foundation, the Howard Hughes Medical Institute, the Swedish Research Council, the Swedish Government Initiative for Strategic Research Institute, the Department of Health and Human Services and the Spectrum Child Health Research Institute.

Stanford’s Department of Pathology also supported the work.

Four research teams receive grants for cancer immunotherapy projects

By Ruthann Richter

The Parker Institute for Cancer Immunotherapy at Stanford has awarded its first round of bench-to-bedside grants to four research teams at the School of Medicine.

These grants are designed for faculty with early-stage ideas in cancer immunotherapy that might not be funded through traditional sources. Each team, consisting of both basic science and clinical investigators, will receive $200,000 over two years.

The awards were selected from a pool of 27 proposals by a committee of Stanford experts led by Crystal Steen, M.D., professor of radiology.

The Parker Institute for Cancer Immunotherapy, is also part of the team.

Ash Alizadeh, MD, PhD, assistant professor of medicine, and Russ Altman, MD, PhD, professor of bioengineering, of genetics and of medicine, are studying cancer antigens — molecules that induce an immune response and that are key to controlling or curing cancer. They are developing a method for predicting which tumor antigens are most likely to be useful in this process. Their team includes graduate student Bin Chen and research scientist Chih Long Liu, PhD.

Wendy Fuei, PhD, assistant professor of obstetrics and gynecology, and her group will be using CO-DEX, an imaging platform invented at Stanford, to determine the key biomarkers that will predict which patients with renal cancer will respond to a form of cancer immunotherapy. Her colleagues are John Lep- pert, MD, assistant professor of urology; senior research scientist Veronica Gonzalez, PhD; and research scientist Nikolay Samusik, PhD.

The institute was established last year as part of an initiative, funded by Silicon Valley pioneer and philanthropist Sean Parker, to develop innovative approaches to cancer by capitalizing on the power of the immune system. Stanford is one of six academic medical centers in the venture, which works through a highly collabora-
New insulin delivery systems for Type 1 diabetes come of age

By Andrew Schwartz

At 19 months old, Jamie Kurtzig was diagnosed with Type 1 diabetes. For the next 10 years, her parents would wake up every three hours during the night to prick their daughter’s finger so they could check her blood glucose level. If her blood glucose was too low, they gave her food to avoid seizures or a loss of consciousness. If it was too high, they gave her insulin to bring the level down to a normal range.

“Too much insulin can cause severe low blood sugars, which can result in seizures, loss of consciousness and, in worst-case scenarios, death. Too little insulin can lead to high blood glucose levels and long-term complications,” said Bruce Buckingham, a professor of pediatrics at the University of California, San Francisco. “Thus, the system’s use in children ages 7 to 14.

For children with Type 1 diabetes, the goal is to become a pharmacist so she can help others, particularly Syrian children. “I feel like I am talking to somebody who could very well be my sister,” Soudi said.

Some student leaders of the campaign said they felt compelled to act in light of the Trump administration’s proposed ban on travel from several Muslim-majority countries, including Syria, that these are human beings worthy of an opportunity,” said Osama El-Gabalah, a first-year Stanford medical student from Jordan, where some 2 million Syrians have sought shelter from their country’s civil war.

“With this system, patients can achieve very reliable and safe overnight glucose control, mitigating overnight highs and lows with minimal manual intervention,” said Buckingham, who treats patients at Packard Children’s. “The improved glucose control dramatically decreases the risk for over-night seizures and long-term complications associated with Type 1 diabetes.

Type 1 diabetes is an autoimmune disease in which the body’s immune system attacks insulin-producing cells in the pancreas. As a result, the body produces little or no insulin, a hormone that brings glucose from the blood-stream into the body’s cells to be used as energy.

Without insulin, the body cannot use glucose as energy. Too much insulin can cause severe low blood glucose levels, which can result in seizures, loss of consciousness and, in worst-case scenarios, death. Too little insulin can lead to high blood glucose levels and long-term complications.”

Clinical trials lead to FDA-approved devices

In September 2016, an article in the Journal of the American Medical Association detailed the successful multicenter trial of a hybrid closed-loop insulin delivery system for patients with Type 1 diabetes over the age of 14. Later that month, the FDA announced approval of the device tested in the study, the Medtronic MiniMed 670G system, for that age group.

The system, commonly referred to as an artificial pancreas, works by wirelessly linking an insulin pump and a glucose monitor. While some of the testing and blood-sugar adjustments can be made by the system, patients must still perform these tasks themselves prior to eating.

Buckingham, a co-author of the article, receives research support from Medtronic. He noted that Stanford conducted the initial studies on this system at a camp for children with diabetes in 2014.

“We are not yet to the point where these systems have been tested and approved in children,” he said. “But they truly mimic all functions of a human pancreas, so there is more work to do.”

Among the challenges: Current hybrid closed-loop systems still require patients to assess the amount of food (carbohydrates) they are eating and deliver an insulin dose through their pump before meals.

Buckingham and his closed-loop team at Stanford continue to test and improve the system. Their efforts include testing and adapting these devices for young children as well as testing systems with different user interfaces and different methodologies that adjust for exercise and insulin delivery at meals.

Helping younger patients and their families

The hybrid closed-loop system has other advantages, as well. Twelve-year-old Jamie Kurtzig, now old enough to want the freedom to do things like attend sleepovers at a friend’s house, still needs to have her insulin delivered based on glucose sensor readings measured every five minutes. He
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New insights into complexity of brain’s navigation system

By Nathan Collins

Just like a driver in a car, the brain needs some basic navigational instruments to get around, and it is not an idle analogy. In fact, scientists have found brain cells that are similar to speedometers, compasses, GPS and even collision warning systems.

That simple analogy, however, may belie the more complex way our brains actually map out the world, Stanford researchers report April 6 in Neuron. While some of the neurons in our internal navigation systems look a lot like speedometers or compasses, many others operate flexibly, each one encoding a dynamic mix of navigational variables, like a compass that somehow transforms into a GPS when driving downtown.

It’s a discovery that could change the way we think about navigation in the brain, said Lisa Giocomo, PhD, assistant professor of neurobiology in the School of Medicine and member of Stanford Bio-X and the Stanford Neurosciences Institute. In fact, it might even challenge one of our most basic assumptions about how neurons work.

Beginning at the boundary

The project began in 2014 when Giocomo and Surya Ganguli, PhD, assistant professor of applied physics, got a Bio-X article on this study.

The Lancet

“Closed-loop devices in what could be the final steps toward that goal are underway in laboratories across the country,” Maahs said. “The work was funded by the New York Stem Cell Foundation, the James S. McDonnell Foundation, the Burnouf-Wellcome Trust, the Alfred P. Sloan Foundation, the McKnight Foundation, the Office of Naval Research the Stanford Center for Mind, Brain and Computation, and Bio-X.”

PhD, professor of pediatrics and of psychiatry and behavioral sciences at the School of Medicine, will lead the pediatric diabetes psychology research team that is investigating how to best help children and their families use such systems, and is partnering with Buckingham on the research.

Improving a child’s quality of life

“Part of our mission is to ensure that the system will be used properly by young patients, meaning that it has the desired impact on both a patient’s health and quality of life,” Hood said.

“To that end, we evaluate the user experience by administering surveys and focus groups, and then we use those responses to generate new strategies and solutions to help the closed-loop system work,” said Ganguli.

Because the pancreas controls glucose both by releasing insulin to lower glucose levels and by releasing glucagon to raise glucose levels, another approach to closed-loop control is to give both insulin and glucagon. Stanford has participated in an NIH-funded, multicenter study that is testing the “bionic pancreas” developed at Boston University. This system has the potential to eliminate the need for carbohydrate counting before meals while also preventing hypoglycemia through the provision of glucagon. The Lancet recently published an article on this study.

David Maahs, MD, the new division chief of pediatrics endocrinology at Packard Children’s, said the program will continue “paving the way for better care, not just for our patients at Packard Children’s, but for people with Type 1 diabetes everywhere.”

Closed-loop continued from page 4

Graduate students, from left, Kiah Hardcastle and Nina Maheshwaranathan, worked with professors Lisa Giocomo and Surya Ganguli on a study of the brain’s navigational neurons.

seed grant to take a closer look at how the brain finds its way around. It was the same year a Nobel Prize was awarded for the discovery of grid cells, specialized neurons that help animals keep track of where they are in their environments. At the time, they were hailed as the brain’s GPS.

But something was off. While some neurons fell within the ballpark of how a grid cell was supposed to behave, most provided only noisy, error-prone naviga-

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Closed-loop continued from page 4

said, “When the system is in auto mode, it monitors my blood sugar every five minutes and keeps up the proper basal rate [of insulin]. Now I only have to check blood sugar four times a day. In the past, I had to check it a lot more, even up to 12 times a day.”

But as they looked around at more navigational neurons, the team found that only a few fit into any pre-defined category.

“We saw all these cell types that didn’t have a name,” Hardcastle said. “They weren’t grid or border, head-direction or speed cells, which are the four main types. This started as an extension of our previous work, but then it really took a left turn.”

Most of the neurons they came across encoded a mix of navigational variables. For example, most neurons that appeared to be grid cells or head-direction cells also tracked speed. Speed cells, meanwhile, were tuned in strange ways. For example, one might fire when a mouse moved either quickly or slowly, but not at intermediate speeds.

Part of our mission is to ensure that the system will be used properly by young patients, meaning that it has the desired impact on both a patient’s health and quality of life,” Hood said.

“At first, the group — now including graduate student N nir Maheshwaranathan — just wanted to see what else boundary cells might be up to,” Hardcastle said. But as they looked around at more navigational neurons, the team found that only a few fit into any pre-defined category.

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And above all, it was hard to iden-

ify any particular set of neuron types, let alone a set that looked like standard navigational instruments. Instead, each neuron seemed to respond a little differ-

ently from each other.

“We didn’t see grid cells or speed cells or head-direction cells,” said Ganguli. “We saw this big continuum.”

How the brain thinks

Giocomo said one of the take-home messages of this work is that there’s still a good mathematical model for the brain’s navigation system. Existing models make assumptions that simply are not compat-

ible with their results. “We need to re-

think basically what the mechanism is.”

There’s a broader issue, too, Ganguli said: The cells of the brain do not neces-

sarily think the way we think, in which case it could be misguided to assume the brain navigates using the same tools — speedometers, compasses, and so forth — as we would.

“The variables that the brain cares about may not be the same as the vari-

ables that the mind cares about. There may be a discrepancy between those. And if there is, then somehow we have to break free of the prejudices of our mind in order to understand the brain,” Ganguli said.

Hardcastle is the Mark and Mary Ste-

vens Interdisciplinary Graduate Fellow, affiliated with the Stanford Neurosci-

ences Institute. Ganguli is also a member of Stanford Bio-X.

The work was funded by the New York Stem Cell Foundation, the James S. McDonnell Foundation, the Burroughs-Wellcome Trust, the Alfred P. Sloan Foundation, the McKnight Foundation, the Office of Naval Research the Stanford Center for Mind, Brain and Computation, and Bio-X.

L.A. CICERO/STANFORD NEWS SERVICE

(Left): Jamie Kurtzig, 12, holding some of her hybrid closed-loop system equipment. (Top right): A left turn is in store.

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“The variables that the brain cares about may not be the same as the vari-

ables that the mind cares about. There may be a discrepancy between those. And if there is, then somehow we have to break free of the prejudices of our mind in order to understand the brain,” Ganguli said.

Hardcastle is the Mark and Mary Ste-

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The work was funded by the New York Stem Cell Foundation, the James S. McDonnell Foundation, the Burroughs-Wellcome Trust, the Alfred P. Sloan Foundation, the McKnight Foundation, the Office of Naval Research the Stanford Center for Mind, Brain and Computation, and Bio-X.

L.A. CICERO/STANFORD NEWS SERVICE

(Left): Jamie Kurtzig, 12, holding some of her hybrid closed-loop system equipment. (Top right): A left turn is in store.

How the brain thinks

Giocomo said one of the take-home messages of this work is that there’s still a good mathematical model for the brain’s navigation system. Existing models make assumptions that simply are not compat-

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(Left): Jamie Kurtzig, 12, holding some of her hybrid closed-loop system equipment. (Top right): A left turn is in store.
one type of breathing: sighing. Knocking out the neurons eliminated sighing but left other modes of breathing unaffected. The discovery was published in Nature in 2016.

Krasnow and Yacke then set out to discover the respiratory role of another subpopulation of about 175 preBötC neurons distinguished by their shared expression of two genetic markers called Cdh9 and Dbx1. The researchers therefore chose to pursue this new idea. "We found that these two processes were linked in some way," said Brunet.

"It’s well-known that epigenetic protein complexes — which epigenetic pathways both affect life span in many animals," said Brunet, who also holds the Michele and Timothy Barakett Endowed Professorship. "We still don’t know why, or whether these two processes were linked in some way." Han and Brunet set out to examine the effect of blocking the activity of a complex of proteins called COMPASS on the metabolism of laboratory roundworms. Roundworms are a popular animal model for longevity studies because of their relatively short life span and ease of care. Together, the COMPASS proteins add chemical tags called methyl groups to DNA, causing the worm to live longer and have more slow breaths associated with chill — or “active” and faster “sniffing” breaths, and more slow breaths associated with chilling out.

Neurons as spies

The researchers surmised that rather than regulating breathing, these neurons were spying on it and reporting their finding to another structure in the brain.

"We expected the long-lived animals in our study would be thinner. Instead, they turned out to be fatter."

Understanding the link

"It’s well-known that epigenetic protein complexes — including the histone modification caused by COMPASS — mimic dietary restriction," Brunet said. "Unlike their sight-deprived brethren, there was no lucana in these mice; their portfolio of breathing variations was greatly diminished."

![Kevin Yacke](https://www.krasnowlab.org/images/staff/yacke.png)

Brunet is a member of Stanford’s Cardiovascular Institute, Cancer Institute and Bio-X. Levy is investigating ways to train the immune system to attack and eradicate cancer cells.

"We are combining the discoveries that stimulate the immune system with new knowledge about the Achilles’ heel of cancer cells,” said Levy, who is the Robert K. and Helen K. Sammy Professor in the School of Medicine. “Great strides have been made in these fields and we hope to bring them together to help patients.”

The NCI Outstanding Investigator Award addresses a problem that many cancer researchers experience: finding a balance between focusing on their science while ensuring that they will have funds to continue their research in the future," said Dinhin Singer, PhD, director of NCIC’s Division of Cancer Biology. She added that providing seven years of uninterrupted funding gives investigators the opportunity to fully develop ambitious cancer research programs.

Chang is a member of Stanford’s Child Health Research Institute, Cancer Institute, Neurosciences Institute, ChEm-H and Bio-X. Levy is a member of the Stanford Cancer Institute and Bio-X. (![](https://www.krasnowlab.org/images/staff/yacke.png))
Random Acts of Flowers delivers smiles, warmth to Stanford Hospital patients

By Jana Chow

When Camille Kennedy enters patient rooms at Stanford Health Care, she is reminded of the isolation she felt when she was admitted to the hospital after an unexpected trip to the Emergency Department.

“When you end up in the hospital, you may find yourself in a place you did not plan to be,” she said. “You think your life is going one way, and it takes a turn.”

These days, Kennedy uses her experience as a patient as motivation to help break through the isolation other patients experience. Kennedy is executive director for Random Acts of Flowers Silicon Valley, an organization that delivers recycled flowers and encouragement to Stanford hospital patients each month, and to patients at hospitals and health care facilities throughout the Bay Area.

Random Acts of Flowers collects unused flowers from florists, grocery stores and flower markets throughout the Bay Area. Volunteers assemble all the flowers into new bouquets, then hand deliver them to patients.

“We are upcycling,” Kennedy said. “Each week, we typically end up with between 4,000 and 8,000 stems of flowers. We use these to create hundreds of bouquets. Most flowers perk up, and we compost anything we don’t use.”

A human connection

While the flowers provide a tangible gift for volunteers to give to patients, Kennedy feels the real value of Random Acts of Flowers is that it delivers a human connection to lonely patients today, tomorrow and for generations to come. “We are trying to combat isolation, and bring people together physically — not just digitally,” she said. “Our volunteers talk with patients, give a handshake or a hug, and always a smile. That interaction and endorphin boost is really terrific for both the patient and the volunteer.”

Many of these volunteers have personal experience with being a patient, and have found healing through helping others.

Between 2009 and 2010, Sandra Bachman spent four months in and out of Stanford Hospital. These were the hardest and scariest days of her life, she said, and now she credits the hospital and staff for saving her life. Volunteering with Random Acts of Flowers has given her an opportunity to redeem her experience at the hospital and to give back.

“We had a compromised quality of life. I had to build up courage before I delivered flowers to each patient,” she said.

By the end of that day, she had created positive memories in a place that had previously filled her with fear. “When patients smile, it makes them and their families and friends smile, and it makes me smile,” she said. “It’s amazing how contagious it is. I get goosebumps every time.”

Moore continued from page 1

after a child in their family benefited from the care of the Children’s Heart Center. “Our grandchild had lifesaving surgery at the hospital, and we would like to help make sure the capability is there for others,” Gordon Moore said. “We are honored to have the Moore family’s visionary partnership as we strive every day to heal humanity through science and compassion, one child and family at a time,” said Christopher Dawes, president and CEO of Lucile Packard Children’s Hospital Stanford. “The Betty Irene Moore Children’s Heart Center will provide world-leading cardiac care to patients today, tomorrow and for generations to come.”

Next wave of innovation and discovery

Over the past 70 years, new surgical techniques and medical therapies, some of which were developed at the Stanford School of Medicine and Packard Children’s, have evolved and helped break through important outcomes for children with almost every type of congenital heart disease. New and emerging therapies are still needed to ensure a healthier future for patients, many of whom continue to face a compromised quality of life and require subsequent surgeries.

“Surgical intervention can repair, but it rarely can truly cure,” said pediatric heart surgeon Frank Hanley, MD, who is also the Lawrence Crowley, MD, Endowed Professor in Child Health at the School of Medicine and executive director of the Betty Irene Moore Children’s Heart Center. “Children who have received complex surgical intervention to repair a cardiac abnormality require careful monitoring and specialized care throughout their life span,” Hanley added. “We imagine a day when a child born with a poorly working aortic valve, rather than undergoing multiple open-heart operations throughout his lifetime, instead receives a replacement valve engineered from his own stem cells. Dr. and Mrs. Moore’s gift comes at a critical juncture — enabling us to advance beyond surgical repair to the discovery of transformative treatments and interventions and, ultimately, to true cures.”

The center has an overall survival rate of 98 percent. Beyond survival alone, the goal is now to ensure an excellent overall outcome — from normal brain function for even the most fragile patients, to the ability for children to perform well in school and to exercise and enjoy an active life into adulthood.

Lifetime of care

“We are committed to providing babies and children with heart disease and their families with the happiest, healthiest lives possible, from the early identification of problems, to expert intervention, and finally to a lifetime of care and support,” said Stephen Roth, MD, MPH, chief of pediatric cardiology and director of the Betty Irene Moore Children’s Heart Center.

“Dr. and Mrs. Moore’s incredible gift will not only bolster our clinical capabilities and research into childhood heart disease now in the Betty Irene Moore Children’s Heart Center, it will also accelerate basic and translational research by Stanford Medicine faculty and scientists to develop more precise techniques to predict, prevent and cure,” said Lloyd Minor, MD, dean of the School of Medicine. “When it comes to achieving precision health, we must think as big as we possibly can — not just about treating disease, but about making and keeping people healthy — and nowhere is this more true than with children.”

In 2017, Packard Children’s will complete its major expansion, becoming the most technologically advanced, family-friendly and environmentally sustainable children’s hospital in the nation. The Moore family’s gift will enable the Children’s Heart Center to expand its state-of-the-art clinical and research facilities, train the future leaders of cardiovascular medicine and surgery, and improve the field of pediatric cardiology and pediatric cardiosurgical surgery through innovative research.

In addition, the center will expand its clinical facilities, including a newly designed outpatient center.

Packard Children’s established the Children’s Heart Center in 2001 to focus more expertise and resources on congenital heart disease, the most common type of birth defect worldwide. Each year, approximately 40,000 children in the United States are born with heart defects, and an additional 25,000 children develop some kind of acquired heart disease.

The center has gained recognition as a national and international destination program for several highly specialized surgical procedures, and is also a full-service cardiology program that cares for all forms of all forms of cardiovascular conditions.

With the leadership of Hanley and Roth, Packard Children’s has 1,000 eligible patients, 25,000 patient visits annually and performs 80 to 90 percent of all cardiac surgical care for children in northern California.

CME center launches webinar series for health professionals on hot topics in medicine

By Ruthann Richter

Stanford Medicine’s Center for Continuing Medical Education is launching a series of free webinars on hot topics in medicine, featuring Stanford experts who will provide guidance to physicians and other health professionals on controversial and challenging issues they may face in their practices. The first webinar, to be offered May 16, will feature two Stanford specialists in pediatric infectious diseases who will discuss challenges of dealing with Zika virus, including surveillance on management and prevention of Zika infection, which can cause serious neurological complications in infants born to mothers infected with the virus. The webinar comes at the start of the warm season, particularly in the southern part of the country, where Zika-carrying mosquitoes are more active and a resurgence of the disease may occur.

The webinar will feature Desiree LLaBeaud, MD, an associate professor of pediatrics whose research focuses on Zika and other mosquito-borne infections. The one-hour session will be moderated by Charles Prober, MD, professor of pediatrics and senior associate dean for medical education at the School of Medicine.

It will be the first in a series of webinars this year, all designed to showcase expertise on timely issues of pressing concern to physicians and other providers, said Linda Baer, the school’s director of CME.

“We are upcycling,” Kennedy said. “Each week, we deliver flowers. We use these to create hundreds of bouquets. We are among the happiest, healthiest lives possible, from the early identification of problems, to expert intervention, and finally to a lifetime of care and support,” said Stephen Roth, MD, MPH, chief of pediatric cardiology and director of the Betty Irene Moore Children’s Heart Center. “Dr. and Mrs. Moore’s gift will not only bolster our clinical capabilities and research into childhood heart disease now in the Betty Irene Moore Children’s Heart Center, it will also accelerate basic and translational research by Stanford Medicine faculty and scientists to develop more precise techniques to predict, prevent and cure,” said Lloyd Minor, MD, dean of the School of Medicine. “When it comes to achieving precision health, we must think as big as we possibly can — not just about treating disease, but about making and keeping people healthy — and nowhere is this more true than with children.”

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The webinar series will be offered through the school’s online CME center. Two topics have been announced for the CME series: Zika virus and other mosquito-borne infections, and the future of pregnancy, assisted reproduction and fertility.

The first webinar, to be offered May 16, will focus on Zika virus. The session will be moderated by Charles Prober, MD, professor of pediatrics and senior associate dean for medical education at the School of Medicine.

Baer said future webinar topics have yet to be finalized, though they could deal with such issues as physician-assisted suicide, medical marijuana and opioid abuse and use.

The course will be valid for 1.0 CME credits. Interested clinicians can sign up for the first webinar at: https://med.stanford.edu/cme/courses/online/webinars/zika_news.html

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The first webinar is designed for primary care physicians, pediatricians, neurologists, infectious disease specialists and obstetrician/gynecologists, as well as nurse practitioners and physician assistants.

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David Schneider appointed chair of microbiology and immunology

By Bruce Goldman

David Schneider, PhD, has been appointed chair of the School of Medicine’s Department of Microbiology and Immunology. His five-year term began April 1.

“This world-class department has seeded a good deal more than its fair share of academic scientists studying microbial pathogenesis and immunology,” said Michael, professor of microbiology and immunology. “I hope to nourish this culture and teach it to our students and postdocs so that we can sustain the innovation and leadership our pioneering faculty has demonstrated.”

Schneider’s current research focuses on quantitatively analyzing sickness during infections and, in particular, on determining how we recover from infections. He has spent the last several years investigating the fundamental causes of resilience to infection and developing mathematical models to predict recovery and well-being after infection.

“Dr. Schneider is a brilliant innovator and respected educator and mentor,” said Lloyd Minor, dean of the School of Medicine. “I am thrilled that he will bring his expertise and perspective to this role.”

Schneider replaces Peter Sarnow, PhD, who has chaired the department since 2010. “Dr. Sarnow brought superb scientific and leadership acumen to the department, advancing cutting-edge research, supporting and developing faculty, and assisting postdoctoral scholars in finding success in academia and industry,” Minor said.

Schneider received his BS in biochemistry from the University of Toronto in 1986 and earned a PhD in molecular biology at the University of California-Berkeley in 1992. He first came to Stanford as a postdoctoral scholar in 1996, between postdoctoral appointments at UCB and UCSF. Between 1997 and 2001, Schneider was a Whitehead Fellow at the Whitehead Institute in Cambridge, Massachusetts. He returned to Stanford as an assistant professor in 2001, was promoted to associate professor in 2008 and became a full professor this year. He is a member of Stanford Bio-X and the Stanford Child Health Research Institute.

Founded nearly 100 years ago, the Department of Microbiology and Immunology numbers more than 25 faculty, 100 postdoctoral scholars and 50 graduate students in addition to two dozen research, administrative and support staff.

“Our department, and Stanford in general, as a place where we aren’t pigeonholed as being certain sorts of scientists,” said Schneider. “When we come up with new ideas, our colleagues don’t say, ‘What do you know about that?’ Rather, they share your excitement and urge you on.”

PEOPLE

OF NOTE

DANIEL CHANG, MD, was promoted to professor of radiation oncology, effective March 1. His clinical focus is on gastrointestinal malignancies, and his research interests include developing stereotactic body radiotherapies for liver tumors and the use of functional imaging to gauge treatment response.

CHITRA DINAKAR, MD, clinical professor of medicine, will serve as an at-large representative on the board of directors of the American Academy of Allergy, Asthma and Immunology. Her term runs from 2017 to 2021. Her research and clinical interests include asthma, food allergies, therapy adherence, and health care disparities and outcomes.

LOUANNE HUDGINS, MD, professor of pediatrics, was named president of the American College of Medical Genetics and Genomics. Her two-year term began April 1. Hudgins is also the medical director of Stanford’s master’s program in American College of Medical Genetics and Genomics pediatrics, was named president of the American College of Medical Genetics and Genomics.

MICHELLE JAMES, PhD, was appointed assistant professor of radiology and of neurology and neurological sciences, effective March 1. Her research focuses on developing and evaluating molecular imaging agents to improve the detection and treatment of brain diseases, particularly Alzheimer’s disease.

DAVID LIANG, MD, PhD, was promoted to professor of medicine, effective March 1. His clinical focus is on Marfan syndrome and other aortic diseases. His research focuses on cardiac imaging, particularly image guidance of procedures.

GEOFFREY LIGHTHALL, MD, PhD, was promoted to professor of anesthesiology, perioperative and pain medicine, effective March 1. His interests include the evaluation and standardization of critically ill patients outside of the ICU and the use of patient simulation as a training tool.

MOUNTAIN LONOKER, MD, the Deane B. and Louise M. Shaw Professor and professor of surgery, is part of a consortium that has received $12 million in funding over three years from the National Institute of Dental and Craniofacial Research to investigate dental, oral and craniofacial health. The funding will support a new California-based project called the Center for Dental, Oral, and Craniofacial Tissue and Organ Reconstruction, C-DOCTOR, which will focus on facilitating tissue-regeneration clinical trials.

SERGIU PASCA, MD, assistant professor of psychiatry and behavioral sciences, has received the 2017 Jordi Folch-Pi Award from the American Society of Neurochemistry. The honor recognizes a young investigator who has significantly contributed to the understanding of neurochemistry and has a high potential for future accomplishments. The award includes a $5,000 prize and was presented this month at the ASN meeting in Arkansas. Pasca’s focus is on generating 3D brain models from stem cells to understand development and capture mechanisms of disease.

VJ PERIYAKOLI, MD, was appointed associate professor of medicine, effective March 1. She is also director of the School of Medicine’s annual meeting. She is the founder of the Letter Project, an effort to promote advance-care planning.

MARIA POLYAKOVA, PhD, assistant professor of health research and policy, has received one of two 2017 Distinguished CSCifo Affiliate Awards in applied economics, big data and vertebrate models of cardiac development.

MARIA GRAZIA RONCAROLO, MD, professor of pediatrics and of medicine, chief of pediatric stem cell transplantation and regenerative medicine, and co-director of the Bas Center for Childhood Cancer and Blood Diseases, will receive the 2017 Outstanding Achievement Award from the American Society of Gene and Cell Therapy, the society’s highest honor. Roncarolo is being recognized for her contributions to the field of gene and cell therapy. She will accept the award in May in Washington, D.C., at the organizing annual meeting.

MANISH SAGGAR, PhD, was appointed assistant professor (research) of psychiatry and behavioral sciences, effective March 1. He is a faculty member at Stanford’s Hasso Plattner Institute of Design, or d.school. He is a computational neuroscientist who examines brain dynamics at rest and during learning.

THOMAS WEISER, MD, was promoted to associate professor of surgery, effective March 1. He is a general and trauma surgeon and a surgical intensivist. Weiser’s research focuses on evaluating postoperative outcomes and barriers to surgical access in resource-poor settings and on developing interventions to improve safety and reliability of care.